

From macroscopic to local molecular thermodynamics

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Molecular thermodynamics reflects the driving forces governing chemical processes, accounting for direct and solvent-mediated interactions and entropic contributions, where the latter originates from both structural flexibility and solvent degrees of freedom. By definition, thermodynamics is a macroscopic approach to molecular energetics as a large number of atomic degrees of freedom or energy states leads to a small number of thermodynamic quantities that can be measured experimentally; this is the domain of statistical thermodynamics. From a predictive perspective, two approaches are available to tackle the problem, molecular simulations (molecular dynamics or Monte-Carlo) and, with special emphasis on solvation features, liquid state theory. Both depend on knowledge of intra-solute and –solvent and solute-solvent interactions which can be determined from force fields or quantum-chemical calculations. In this context, the question arises whether these macroscopic thermodynamic features can be mapped to *local*, i.e. atom or group based components that would allow for an analysis of the impact of local changes on macroscopic data, a key feature of molecular design.

In this talk, the perspective of liquid state theory, more specifically the integral equation approach known as 3D RISM (reference interaction site model) theory is outlined for the prediction of thermodynamic quantities and their localization. Starting with the basic elements and practically useful approximations, it will be demonstrated that predictive models can be developed by combining 3D RISM with quantum chemistry in the form of the embedded cluster (EC-)RISM method [1-3]. Following-up on these benchmarks, physically sound localization methods are outlined and discussed. In particular, a local picture of hydration thermodynamics is developed which can be utilized for drug discovery [4], the energetic and entropic components of solvation thermodynamics are analyzed [5], and preliminary results are presented for the localization of binding free energies in host-guest complexes [6]. The talk concludes with a perspective on exploiting local thermodynamics in the context of machine learning for addressing the molecular design challenge.

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